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Signed Stephen Hordley

Dated 5 January 2004

Patents Form 1/77

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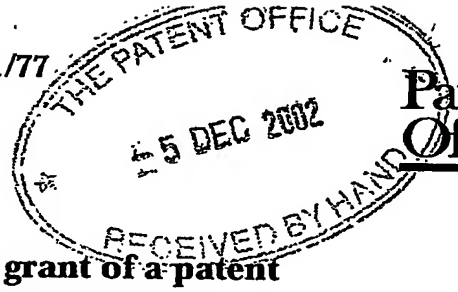

The Patent Office

060EC02 E788979-3 D02890
P01/7700 0.00-0228430.5

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference

REP07359GB

2. Patent application number
(The Patent Office will fill in this part)

0228430.5

05 DEC 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
Little Chesterford
Saffron Walden
CB10 1XL

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

08423733001

4. Title of the invention

RESOLUTION PROCESS

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)*

745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	4
Claim(s)	1
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
5 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry
020 7377 1377

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Notes

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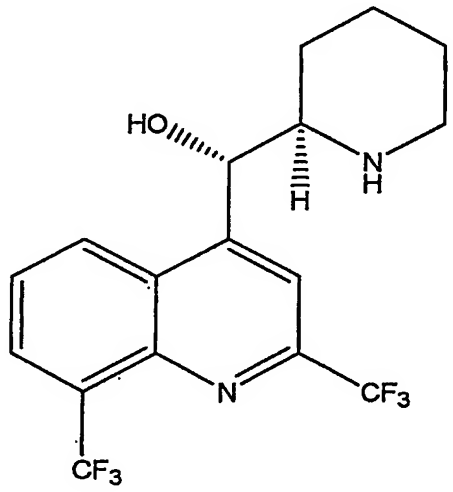
RESOLUTION PROCESS

Field of the Invention

The present invention relates to a process for the manufacture of the single enantiomers of mefloquine.

Background to the Invention

Mefloquine [*erythro*-α-2'-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol] is a chiral drug substance and synthetic analogue of quinine, originally developed to replace existing anti-malarials where resistance had developed. Although mefloquine is marketed as a racemic mixture, both enantiomers of the drug have been shown to demonstrate different biological activities. (+)-mefloquine has been disclosed (EP-A-0966285) for the treatment of malaria with reduced side-effects. (-)-Mefloquine has been disclosed (EP-A-0975345 and EP-A-01107761) to block purinergic receptors and to have utility in the treatment of movement and neurodegenerative disorders. WO-A-02/019994 discloses that (+)-(11S, 12R)-*erythro*-mefloquine (**1**)



(1)

is the preferred enantiomer for the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, Crohn's disease, systemic lupus erythematosis (SLE), ulcerative colitis, chronic obstructive pulmonary disease (COPD) and asthma.

An efficient and reliable method for the preparation of the individual enantiomers of mefloquine is desirable. As racemic mefloquine is readily

available, a classical resolution process, involving separation of diastereoisomeric salts by selective crystallisation is described.

Essentially only two routes to the enantiomers of mefloquine are published, but neither is suitable for the preparation of optically pure mefloquine on a commercial scale. Carroll and Blackwell (*Journal of Medicinal Chemistry*, 1974, **17**, 210) resolved the enantiomers of mefloquine by crystallisation with (+)- and (-)-3-bromo-8-camphorsulphonic acid ammonium salts in aqueous methanol. More recently, the asymmetric synthesis of either enantiomer of mefloquine by hydrogenation of a key pyridyl ketone in the presence of a variety of rhodium diphosphine catalysts has been reported (EP-A-0553778 and EP-A-0582632). The intermediate chiral alcohol could be prepared in up to 99% yield and 95% enantiomeric excess. Subsequent hydrogenation over platinum afforded enantiomerically enriched mefloquine in high yield.

Summary of the Invention

This invention is based on the surprising discovery that racemic mefloquine can be resolved efficiently, using the substantially single enantiomers of *O,O*-di-*p*-toluoyltartaric acid (DTTA) as a resolving agent.

Description of the Invention

The process of this invention may be carried out under conditions that are generally known to those skilled in the art of classical optical resolution methods. Resolutions utilising DTTA are classically carried out in an alcoholic solvent such as methanol or ethanol. However, in the case of mefloquine, methanol, ethanol and butanol all failed to provide a satisfactory resolution. Screening of several solvents indicated that esters, ketones and halogenated solvents, including alkyl alkanoates and haloalkanes, e.g. dichloromethane or isopropyl or ethyl acetate, are capable of providing a single enantiomer of mefloquine in high yield and good enantiomeric excess. Further experiments with ethyl acetate as a solvent indicated that the yield and enantiomeric excess could be further improved by increasing dilution. In a typical experiment, mefloquine was dissolved in ethyl acetate then treated with a solution of *O,O*-di-*p*-toluoyl-L-tartaric acid monohydrate (1.0 mol equivalent). The resulting solution was

allowed to stand until precipitation occurred. Collection of the solid produced the (+)-mefloquine DTTA salt in 40% yield and 98% enantiomeric excess.

Since both enantiomers of DTTA are readily available in quantity, either can be used to effect the resolution depending on which enantiomer of mefloquine is required. Thus, (-)-mefloquine DTTA salt could be prepared in a similar yield and optical purity utilizing *O,O*-di-*p*-toluoyl-D-tartaric acid monohydrate as the resolving agent.

This resolving agent may also be used to increase the optical purity of enantiomerically-enriched mefloquine. Thus, when both enantiomers of mefloquine are required, the processes described above can be compressed, one enantiomer being recovered by the resolution and the opposite enantiomer being extracted from the mother liquors of the resolution. In practice, when (+)-mefloquine DTTA salt is recovered as described above, the mother liquors remaining are processed to isolate mefloquine free base enriched in the (-)-isomer, which is then purified by treatment with *O,O*-di-*p*-toluoyl-D-tartaric acid monohydrate and crystallization of the resultant salt.

Other beneficial aspects of the process of the present invention have been identified and these can be summarized as follows:

1. The DTTA resolving agent can be easily recovered in a state of high purity, such that it can be re-used in one or more subsequent resolution processes.
2. If desired, less than 1.0 molar equivalent of DTTA may be used in the process.
3. Efficient resolution can be achieved when the input racemic mefloquine is contaminated with the isomeric threo-mefloquine.

A substantially single enantiomer that is used in or produced by the process of the invention may be in at least 80% ee, preferably at least 90% ee, more preferably at least 95% ee, and most preferably at least 98% ee.

The present invention is illustrated by the following Examples.

Example 1 **(+)-(11S, 12R)-*Erythro*-mefloquine, *O,O*-(-)-ditoluoyl-L-tartrate salt**

To a solution of (±)-*erythro*-mefloquine (10.0 g mmol, 26.6 mmol) in ethylacetate (440 mL) was added a solution of *O,O*-(-)-ditoluoyl-L-tartaric acid (10.2 g, 26.4 mmol, 1.0 equiv.) in ethyl acetate (80 mL). This corresponds to a 4% solution w/v. The resulting solution was stoppered and stirred at room temperature for 3 hours. The white crystalline solid formed was filtered off and washed with ethyl acetate (2 x 200 mL), and dried under vacuum to furnish 8.69 g, of product. The solid was then suspended in ethyl acetate (220 mL) and heated under reflux for 1 hour. On cooling the solid was filtered, washed with ethyl acetate (100 mL) and dried under vacuum to furnish the product as a colourless solid 6.88 g, yield 34 %, 98.3 % ee.

Example 2 **(+) – (11S, 12R)-*Erythro*-mefloquine**

The isolated product of Example 1 (6.66 g, 8.74 mmol) was suspended in methanol (22 mL). A solution of water (92 mL) and 22 % sodium hydroxide (6.7 mL) was charged over 1 hour until a final pH 14 was reached. The suspension was stirred at room temperature for 2.5 hours and the suspension filtered, washed with water (2 x 50 mL) and dried under vacuum to furnish the (+)-(11S, 12R)-*erythro*-mefloquine as a colourless solid, 2.94 g, yield 89 %, 98.8 % ee.

Example 3 **(+)-(11S, 12R)-*Erythro*-mefloquine, hydrochloride salt**

The isolated product of Example 2 (2.78 g, 7.34 mmol) was dissolved in diisopropyl ether (110 mL) and stirred at room temperature. A solution of 2 N hydrochloric acid in diethyl ether (4 mL) was added dropwise with stirring and the resulting suspension stirred at room temperature for 1 hour. The suspension was filtered and the solid washed with diisopropyl ether (2 x 100 mL) and dried to furnish (+)-erythro mefloquine hydrochloride as a colourless solid, 2.86 g, yield 94 %, >99 % ee.

CLAIMS

1. A process for increasing the optical purity of a mixture of enantiomers of mefloquine, using a substantially single enantiomer of a *O,O*-di-*p*-aroyltartaric acid as a resolving agent.

2. A process for preparing a substantially single enantiomer of mefloquine, which proceeds by means of resolution of racemic mefloquine using a substantially single enantiomer of a *O,O*-di-*p*-aroyltartaric acid as a resolving agent.

3. A process according to claim 2, for preparing substantially single enantiomer (+)-mefloquine, which uses *O,O*-di-*p*-toluoyl-L-tartaric acid as the resolving agent.

4. A process according to claim 2, for preparing substantially single enantiomer (-)-mefloquine or a pharmaceutically acceptable salt thereof, which uses *O,O*-di-*p*-toluoyl-D-tartaric acid as the resolving agent.

5. A process according to any preceding claim, wherein the mefloquine is contaminated with *threo*-mefloquine.

6. A process according to any preceding claim, which is conducted in a solvent selected from esters, ketones and halogenated solvents.

7. A process according to any preceding claim, which further comprises conversion of the salt obtained by the resolution to the free base form of mefloquine or a pharmaceutically acceptable salt thereof.